

## Organophosphate Pesticides: Specific Metabolites

### General Information

These metabolites differ from the dialkyl phosphates because they are more specific in their reference to the parent compound. The mechanism of action and pathways of exposure to the general population are similar to those of the other organophosphate pesticides (see section above titled “Organophosphate Pesticides: Dialkyl Phosphate Metabolites”). Malathion, chlorpyrifos, and diazinon are commonly used organophosphate insecticides in the United States. Malathion and several other pesticides are used to control adult mosquitoes. Chlorpyrifos accounted for 20% of total insecticides use in the United States in 1997, but its use is likely to decrease over time as a result of provisions in the Food Quality and Protection Act of 1996. Parathion use will be banned after 2003.

This *Report* provides measurements for the metabolites of six organophosphate pesticides. Table 144 shows the parent organophosphate pesticides and their metabolites. For example, malathion metabolizes to malathion dicarboxylic acid. *Para*-Nitrophenol can result from the metabolism of several organophosphate pesticides: parathion, ethyl p-nitrophenyl thionobenzenephosphonate (EPN), 4-nitroanisole, nitrofen, and nitrobenzene. Chlorpyrifos and chlorpyrifos methyl are metabolized to 3,5,6-trichloro-2-pyridinol. In addition to reflecting exposure to the parent insecticide, the level of the metabolite in a person’s urine may also reflect exposure to the metabolite if it was present in the person’s environment. Information about external exposure (environmental levels) and health effects of specific organophosphate pesticides is available from the EPA

IRIS Web site at <http://www.epa.gov/iris> and from ATSDR at <http://www.atsdr.cdc.gov/toxprofiles>.

### *Interpreting Selected Urine Organophosphate Metabolite Levels Reported in the Tables*

Urine levels of the metabolites of six organophosphate pesticides were measured in a subsample of NHANES participants aged 6 years and older. Subsamples were randomly selected within the specified age range to be a representative sample of the U.S. population. Measuring these chemicals at these levels is possible because of advances in analytical chemistry. Finding a measurable amount of one or more metabolites in the urine does not mean that the levels of the organophosphate pesticide cause an adverse health effect. Whether organophosphate pesticides at the levels reported here are causes for health concern is not known; more research is needed.

Generally recognized guidelines for urine levels of these metabolites are not available. However, urinary measurements of the specific metabolites of the organophosphate pesticides can be used to monitor worker exposure. As with the dialkyl phosphate metabolites, the specific metabolites can be measured at low levels of exposure that do not cause depression of cholinesterase activity. The U.S. FDA, U.S. EPA, and OSHA have developed criteria on the allowable levels of these chemicals in foods, the environment, and the workplace. These data provide physicians with a reference range so that they can determine whether people have been exposed to higher levels of these select organophosphate pesticides than those found in the general population. Tables 145-152 summarize the results of these measurements. These data will help scientists plan and conduct research about exposure to these chemicals and their health effects.

**Table 144. Organophosphate pesticides: specific metabolites**

Organophosphate pesticide (CAS number)	Primary urinary metabolite (CAS number)
Malathion (121-75-5)	Malathion dicarboxylic acid (1190-28-9)
Parathion (56-38-2)	<i>para</i> -Nitrophenol (100-02-7)
Methyl parathion (298-00-0)	<i>para</i> -Nitrophenol (100-02-7)
Chlorpyrifos (2921-88-2)	3,5,6-Trichloro-2-pyridinol (6515-38-4)
Chlorpyrifos methyl (5598-13-0)	3,5,6-Trichloro-2-pyridinol (6515-38-4)
Diazinon (333-41-5)	2-Isopropyl-4-methyl-6-hydroxypyrimidine (2814-20-2)

## Malathion dicarboxylic acid

CAS No. 1190-28-9

Metabolite of malathion (CAS No. 121-75-5)

Urinary levels of malathion dicarboxylic acid at the 95<sup>th</sup> percentile for the 6-11-year-old group are severalfold lower than levels that were measured in Minnesota children (aged 3-13, adjusted for sociodemographic variables) in 1997 (Adgate, 2001). In this Minnesota study, children from an urban setting had urinary levels of malathion dicarboxylic acid that were similar to levels in children from a non-urban setting.

**Table 145. Malathion dicarboxylic acid**

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. population aged 6 to 59 years, National Health and Nutrition Examination Survey, 1999-2000.

	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval)						Sample size
		10th	25th	50th	75th	90th	95th	
<b>Total, age 6-59</b>	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	1920
<b>Age group</b>								
6-11 years	*	< LOD	< LOD	< LOD	< LOD	< LOD	2.80 (<LOD-5.50)	453
12-19 years	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	660
20-59 years	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	807
<b>Gender</b>								
Males	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	937
Females	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	983
<b>Race/ethnicity</b>								
Mexican Americans	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	680
Non-Hispanic blacks	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	498
Non-Hispanic whites	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	579

< LOD means less than the limit of detection, which averaged 0.29 µg/L (SD 0.78, maximum value 2.64).

\* Not calculated. Proportion of results below limit of detection was too high to provide a valid result.

**Table 146. Malathion dicarboxylic acid (creatinine adjusted)**

Geometric mean and selected percentiles of urine concentrations (in µg/gram of creatinine) for the U.S. population aged 6 to 59 years, National Health and Nutrition Examination Survey, 1999-2000.

	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval)						Sample size
		10th	25th	50th	75th	90th	95th	
<b>Total, age 6-59</b>	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	1920
<b>Age group</b>								
6-11 years	*	< LOD	< LOD	< LOD	< LOD	< LOD	3.74 (2.27-4.65)	453
12-19 years	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	660
20-59 years	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	807
<b>Gender</b>								
Males	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	937
Females	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	983
<b>Race/ethnicity</b>								
Mexican Americans	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	680
Non-Hispanic blacks	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	498
Non-Hispanic whites	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	579

< LOD means less than the limit of detection (see previous table).

\* Not calculated. Proportion of results below limit of detection was too high to provide a valid result.

## para-Nitrophenol

CAS No. 100-02-7

Metabolite of parathion and other pesticides (CAS No. 56-38-2)

The *para*-nitrophenol levels in this *Report* are similar to levels measured in a non-random subsample from NHANES III (1988-1994) participants (Hill et al., 1995). The urinary *para*-nitrophenol levels in this *Report* for the group aged 6-11 years are lower than levels measured in children residing in households close to pesticide-treated farmlands but similar to levels in children residing farther away (Fenske et al., 2002). Inappropriate residential application of methylparathion led to a 25-fold increase in the median urinary PNP level of the people living in those residences (Esteban et al., 1996).

In a study of workers who handle parathion, end-of-shift urine PNP levels ranged from 190-410 µg/gram of creatinine (Len and Lewalter, 1999), or about 100 times higher than levels documented in this *Report*. ACGIH recommends a BEI of 0.5 mg/gram of creatinine for workers at the end of shift. In 1975, the World Health Organization indicated that no depression of cholinesterase activity occurred from parathion exposure when urinary PNP levels were below 2 mg/L (2000 µg/L) (Lauwerys and Hoet, 2001). All PNP values in this *Report* are much lower than these levels of concern for workers.

**Table 147. *para*-Nitrophenol**

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. population aged 6 to 59 years, National Health and Nutrition Examination Survey, 1999-2000.

	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval)						Sample size
		10th	25th	50th	75th	90th	95th	
<b>Total, age 6-59</b>	*	< LOD	< LOD	< LOD	< LOD	2.40 (1.70-3.80)	5.00 (3.30-9.00)	1989
<b>Age group</b>								
6-11 years	*	< LOD	< LOD	< LOD	< LOD	2.63 (1.90-3.80)	4.20 (2.70-6.40)	479
12-19 years	*	< LOD	< LOD	< LOD	< LOD	3.40 (1.70-5.70)	5.70 (2.60-19.0)	680
20-59 years	*	< LOD	< LOD	< LOD	< LOD	2.30 (1.60-4.00)	4.50 (2.50-9.20)	830
<b>Gender</b>								
Males	*	< LOD	< LOD	< LOD	< LOD	2.40 (1.60-4.00)	4.40 (2.60-11.0)	971
Females	*	< LOD	< LOD	< LOD	< LOD	2.50 (1.70-4.20)	5.20 (3.00-9.50)	1018
<b>Race/ethnicity</b>								
Mexican Americans	*	< LOD	< LOD	< LOD	< LOD	5.80 (3.00-20.0)	21.0 (4.99-31.0)	695
Non-Hispanic blacks	*	< LOD	< LOD	< LOD	< LOD	2.90 (1.90-4.70)	4.80 (2.70-9.00)	518
Non-Hispanic whites	*	< LOD	< LOD	< LOD	< LOD	2.10 (<LOD-3.80)	4.20 (2.20-9.50)	602

< LOD means less than the limit of detection, which is 0.8 µg/L.

\* Not calculated. Proportion of results below limit of detection was too high to provide a valid result.

**Table 148. *para*-Nitrophenol (creatinine adjusted)**

Geometric mean and selected percentiles of urine concentrations (in µg/gram of creatinine) for the U.S. population aged 6 to 59 years, National Health and Nutrition Examination Survey, 1999-2000.

	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval)						Sample size
		10th	25th	50th	75th	90th	95th	
<b>Total, age 6-59</b>	*	< LOD	< LOD	< LOD	< LOD	2.08 (1.43-3.37)	4.20 (2.55-7.64)	1989
<b>Age group</b>								
6-11 years	*	< LOD	< LOD	< LOD	< LOD	2.80 (1.98-3.54)	4.20 (3.33-6.67)	479
12-19 years	*	< LOD	< LOD	< LOD	< LOD	1.79 (1.07-3.44)	4.00 (1.57-7.29)	680
20-59 years	*	< LOD	< LOD	< LOD	< LOD	2.00 (1.33-3.37)	4.29 (2.43-10.2)	830
<b>Gender</b>								
Males	*	< LOD	< LOD	< LOD	< LOD	1.90 (1.12-3.00)	3.39 (1.90-7.55)	971
Females	*	< LOD	< LOD	< LOD	< LOD	2.22 (1.67-4.28)	6.90 (3.54-12.3)	1018
<b>Race/ethnicity</b>								
Mexican Americans	*	< LOD	< LOD	< LOD	< LOD	4.80 (2.75-14.9)	17.4 (4.80-34.9)	695
Non-Hispanic blacks	*	< LOD	< LOD	< LOD	< LOD	2.07 (1.40-3.26)	3.71 (2.17-5.16)	518
Non-Hispanic whites	*	< LOD	< LOD	< LOD	< LOD	1.94 (1.17-3.54)	3.75 (2.08-7.64)	602

< LOD means less than the limit of detection (see previous table).

\* Not calculated. Proportion of results below limit of detection was too high to provide a valid result.

## 3,5,6-Trichloro-2-pyridinol

CAS No. 6515-38-4

Metabolite of chlorpyrifos (CAS No. 2921-88-2)

The 3,5,6-trichloro-2-pyridinol (TCPy) levels shown in this *Report* are similar to levels measured in a non-random subsample from NHANES III (1988-1994) participants (Hill et al., 1995). The urinary TCPy levels for the group aged 20 years and older are lower than or similar to levels found in other studies (Byrne et al., 1998; Bartels and Kastl, 1992). In one study from 1996, urinary TCPy measured in Maryland adults were about three times higher than levels for adults documented in this *Report* (MacIntosh et al., 1999). These higher levels may represent variations in the local use of pesticides,

participant selection, and sampling methods. The seasonal use of pesticides can contribute to differences in TCPy levels as well since urine TCPy levels were found to be higher during the spring and summer than during the fall and winter (MacIntosh et al., 1999). Levels in applicators of chlorpyrifos-methyl and chlorpyrifos can be greater than 40-fold higher than levels in control subjects (Lauwerys and Hoet, 2001).

The urinary TCPy levels for children aged 6-11 years in this *Report* are similar to levels measured in 1997 in a group of non-urban Minnesota children (aged 3-13 years, adjusted by their sociodemographic variables) (Adgate et al., 2001). In this latter study, children from an urban setting had levels that were 1.5 times higher than levels

**Table 149. 3,5,6-Trichloro-2-pyridinol**

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. population aged 6 to 59 years, National Health and Nutrition Examination Survey, 1999-2000.

	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval)						Sample size
		10th	25th	50th	75th	90th	95th	
<b>Total, age 6-59</b>	1.77 (1.56-2.01)	< LOD	.870 (.770-.990)	1.70 (1.50-2.00)	3.50 (2.70-4.50)	7.30 (5.40-9.40)	9.90 (7.60-14.0)	1994
<b>Age group</b>								
6-11 years	2.88 (2.13-3.88)	.780 (.630-.970)	1.20 (1.10-1.70)	2.70 (1.80-4.20)	6.90 (3.70-9.40)	11.0 (7.70-17.0)	16.0 (10.0-24.0)	481
12-19 years	2.37 (2.00-2.81)	.790 (.700-.890)	1.20 (1.00-1.50)	2.10 (1.60-2.60)	4.50 (3.10-5.70)	8.00 (5.70-12.0)	12.5 (8.40-23.0)	681
20-59 years	1.53 (1.36-1.73)	< LOD	.750 (.620-.880)	1.50 (1.20-1.60)	2.80 (2.40-3.70)	5.90 (4.30-7.94)	8.60 (6.30-12.0)	832
<b>Gender</b>								
Males	1.92 (1.67-2.21)	.450 (<LOD-.630)	1.00 (.810-1.10)	1.90 (1.60-2.20)	3.50 (2.90-4.60)	7.30 (5.60-9.40)	9.90 (7.90-14.0)	972
Females	1.63 (1.41-1.88)	< LOD	.770 (.650-.870)	1.50 (1.20-1.70)	3.30 (2.50-4.70)	7.20 (4.86-9.70)	10.0 (6.90-16.0)	1022
<b>Race/ethnicity</b>								
Mexican Americans	1.61 (1.37-1.90)	< LOD	.870 (.610-1.10)	1.67 (1.30-2.10)	3.20 (2.60-3.80)	5.00 (4.00-6.40)	7.40 (5.50-12.0)	697
Non-Hispanic blacks	2.17 (1.71-2.76)	.560 (<LOD-.800)	1.00 (.840-1.20)	1.90 (1.50-2.50)	4.20 (2.80-7.30)	9.40 (6.70-12.0)	13.0 (9.60-25.0)	521
Non-Hispanic whites	1.76 (1.52-2.03)	.420 (<LOD-.600)	.880 (.760-1.10)	1.60 (1.50-2.00)	3.40 (2.60-4.57)	7.10 (4.70-9.60)	10.0 (6.90-16.0)	601

< LOD means less than the limit of detection, which is 0.4 µg/L.

of children from a non-urban setting. Fenske et al. (2002) found that children residing either near pesticide-treated farmland or in households where pesticide use occurred had higher urinary TCPy levels than those living in surroundings where less pesticide exposure occurred.

Geometric mean levels of the demographic groups were compared after adjustment for the covariates of race/ethnicity, age, gender, and urinary creatinine. The group aged 6-11 years had slightly higher urine TCPy levels than either the 12-19 year or 20 years and older age groups. Further research is necessary to evaluate this difference in TCPy levels among age groups. There were no differences in TCPy levels among genders or racial/ethnic categories.

**Table 150. 3,5,6-Trichloro-2-pyridinol (creatinine adjusted)**

Geometric mean and selected percentiles of urine concentrations (in µg/gram of creatinine) for the U.S. population aged 6 to 59 years, National Health and Nutrition Examination Survey, 1999-2000.

	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval)						Sample size
		10th	25th	50th	75th	90th	95th	
<b>Total, age 6-59</b>	1.58 (1.41-1.77)	< LOD	.870 (.757-.966)	1.47 (1.31-1.65)	2.85 (2.22-3.38)	5.43 (4.26-6.62)	8.42 (6.27-11.6)	1994
<b>Age group</b>								
6-11 years	3.11 (2.39-4.05)	.864 (.535-1.36)	1.64 (1.18-2.05)	3.20 (2.05-4.35)	6.37 (4.21-8.19)	10.1 (6.75-16.0)	14.0 (8.74-21.7)	481
12-19 years	1.60 (1.40-1.83)	.608 (.549-.698)	.930 (.816-1.08)	1.45 (1.24-1.69)	2.58 (2.03-3.56)	4.82 (3.92-5.57)	6.16 (4.95-9.76)	681
20-59 years	1.41 (1.26-1.58)	< LOD	.786 (.694-.892)	1.33 (1.16-1.50)	2.37 (1.96-2.86)	4.25 (3.29-5.63)	6.42 (4.98-10.7)	832
<b>Gender</b>								
Males	1.48 (1.30-1.67)	.473 (.402-.557)	.796 (.698-.914)	1.44 (1.27-1.61)	2.52 (2.09-3.24)	4.95 (3.98-6.27)	7.63 (5.73-10.7)	972
Females	1.69 (1.49-1.91)	< LOD	.913 (.816-1.00)	1.51 (1.33-1.74)	2.96 (2.37-3.70)	5.63 (4.25-7.19)	8.44 (6.25-13.1)	1022
<b>Race/ethnicity</b>								
Mexican Americans	1.46 (1.27-1.67)	< LOD	.859 (.737-.994)	1.44 (1.16-1.73)	2.38 (2.11-2.86)	3.82 (3.33-5.07)	5.79 (4.35-9.04)	697
Non-Hispanic blacks	1.47 (1.18-1.84)	.435 (.405-.513)	.733 (.591-.917)	1.33 (1.02-1.76)	2.86 (1.84-4.38)	5.88 (4.26-8.93)	8.93 (5.91-13.7)	521
Non-Hispanic whites	1.66 (1.46-1.89)	.543 (.462-.675)	.909 (.802-1.03)	1.55 (1.33-1.74)	2.93 (2.14-3.68)	5.50 (4.21-6.95)	8.44 (6.14-12.5)	601

< LOD means less than the limit of detection (see previous table).

## 2-Isopropyl-4-methyl-6-hydroxypyrimidine

CAS No. 2814-20-2

Metabolite of diazinon (CAS No. 333-41-5)

Urinary concentrations of 2-isopropyl-4-methyl-6-hydroxypyrimidine from the NHANES 1999-2000 subsample are similar to those reported previously in a non-random sample from the U.S. population (Baker et al., 2000).

**Table 151. 2-Isopropyl-4-methyl-6-hydroxypyrimidine**

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. population aged 6 to 59 years, National Health and Nutrition Examination Survey, 1999-2000.

	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval)						Sample size
		10th	25th	50th	75th	90th	95th	
<b>Total, age 6-59</b>	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	1842
<b>Age group</b>								
6-11 years	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	454
12-19 years	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	632
20-59 years	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	756
<b>Gender</b>								
Males	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	894
Females	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	948
<b>Race/ethnicity</b>								
Mexican Americans	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	644
Non-Hispanic blacks	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	484
Non-Hispanic whites	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	553

< LOD means less than the limit of detection, which averaged 2.0 µg/L (SD 1.7, maximum value 7.20).

\* Not calculated. Proportion of results below limit of detection was too high to provide a valid result.



**Table 152. 2-Isopropyl-4-methyl-6-hydroxypyrimidine (creatinine adjusted)**

Geometric mean and selected percentiles of urine concentrations (in µg/gram of creatinine) for the U.S. population aged 6 to 59 years, National Health and Nutrition Examination Survey, 1999-2000.

	Geometric mean (95% conf. interval)	Selected percentiles (95% confidence interval)						Sample size
		10th	25th	50th	75th	90th	95th	
<b>Total, age 6-59</b>	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	1842
<b>Age group</b>								
6-11 years	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	454
12-19 years	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	632
20-59 years	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	756
<b>Gender</b>								
Males	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	894
Females	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	948
<b>Race/ethnicity</b>								
Mexican Americans	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	644
Non-Hispanic blacks	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	484
Non-Hispanic whites	*	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	553

< LOD means less than the limit of detection (see previous table).

\* Not calculated. Proportion of results below limit of detection was too high to provide a valid result.

